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Rapid entry into heterocycle-fused benzylic azepines and azocines via directed metallation/ring-closing metathesis

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ABSTRACT

The efficient synthesis of a range of heterocycle-fused benzylic azepine and azocine derivatives is reported, employing a directed metallation/ruthenium-catalysed ring-closing metathesis approach. A base-mediated tautomerisation approach can be used to access both the azepine and azocine derivatives from the same starting material.

The efficient construction of medium sized nitrogen-containing rings is an ongoing challenge for synthetic chemists, as the entropic penalty for ring closure is typically higher than for five- and six-membered systems. Nonetheless, fused nitrogen-containing seven- (azepine) and eight- (azocine) membered ring systems are common in Nature, being found in a number of bioactive molecules and pharmaceuticals. These include natural products such as the galanthamine family[1] and apparicine,[2] as well as promising medicinal chemistry targets[3,4] (Fig. 1).

Due to their attractive structures, fused 2-benzazocines have been investigated previously in the literature, with methods such as radical chain insertion,[5] electrophilic cyclisation[6] and Schmidt rearrangement[7] being employed to build the saturated ring. A powerful method for synthesising medium sized nitrogen-containing ring systems is the ruthenium-catalysed ring-closing metathesis reaction (RCM),[8] which has been widely utilised for the synthesis of benzo-fused azepines and azocines. However one area that remains poorly developed is the synthesis of heterocycle-fused ring systems, in particular those which contain key molecular binding sites such as pyrimidines, pyridines and azoles. As part of our ongoing interest into the synthesis of partially saturated fused ring systems,[9] we previously described the efficient construction of various heterocycle-fused 1-azepine derivatives.[10] As detailed in Figure 1, fused 2-azepines and 2-azocines are an important target in both natural product and medicinal chemistry. To this point, the majority of attention amongst academic groups has been directed at the synthesis of 1-benzazepine derivatives by RCM,[11] including some examples of heterocycle-fused 1-benzazepines.[12] With this in mind, we embarked upon a project to investigate the efficient construction of fused 2-azepines and -azocines. Our initial aim was to build the saturated ring through a directed metallation/ring-closing metathesis strategy, as described previously by Snieckus and co-workers for the synthesis of benzazepines and benzazocine derivatives[13] (Scheme 1).

Although this method was reported to work well for substituted phenyl derivatives, heteroatom-containing examples were not explored. We anticipated that moving from simple phenyl derivatives to heterocycles would present a number of challenges, in particular the sensitivity of the substrates to metallation. Further-

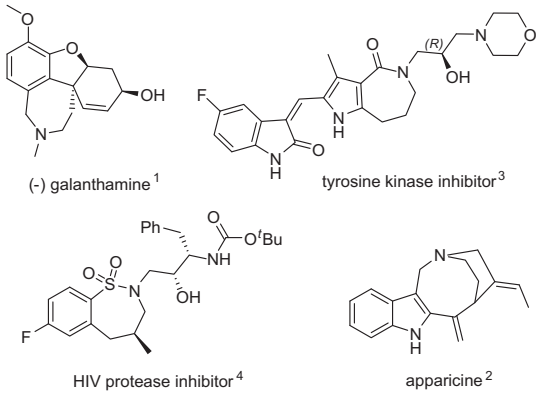

Figure 1. Examples of fused azepines and azocines found in nature and in medicinal chemistry.

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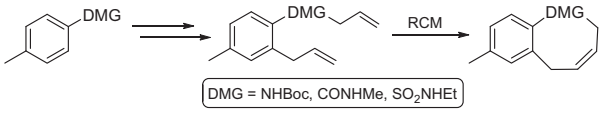
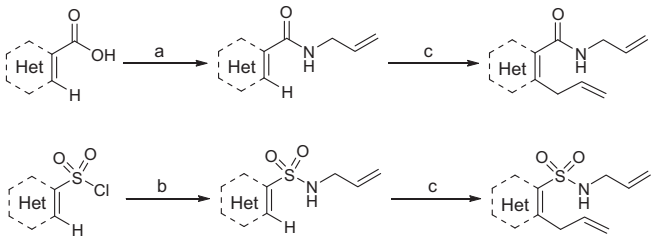


Scheme 1. Directed metallation/RCM strategy described by Snieckus.

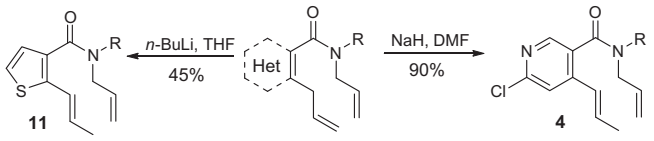
more, we aimed to synthesise RCM products containing handles for further elaboration (e.g., halogens for Pd-catalysed cross-couplings), which could potentially pose problems with the competitive metal–halogen exchange pathway. With these factors in mind, we began our studies into the synthesis of the RCM precursors. Allyl amides and allyl sulfonamides were intially chosen as the metallation directing groups, as these could easily be accessed in near quantitative yields from the carboxylic acid and sulfonyl chlorides, respectively. In the case of carboxylic acid derivatives, formation of the acid chloride with oxalyl chloride prior to treatment with allylamine proved to be cleaner and quicker than direct amide coupling methods. The *C*-allyl group could then be inserted by *ortho*-metallation with *n*-BuLi, followed by quenching with allyl bromide. In most cases, it was necessary to perform a transmetallation with copper(I) bromide prior to the addition of the electrophile in order to attenuate the high basicity of the lithium species. The more sensitive pyridine substrates turned out not to be stable to *n*-BuLi, however, metallation could be readily performed using milder TMPMgCl·LiCl (TMP = 2,2,6,6-tetramethylpiperidide).[14] This had the added benefit that carbon–halogen bond insertion did not occur with this base, allowing aryl bromide substrates to be accessed. Once C-allylation had been performed, the RCM reaction could be carried out directly, or the amide could be N-protected under standard conditions in cases where the free NH turned out to be detrimental to RCM (Scheme 2).

Pleasingly, this approach worked well for a range of heteroaryl substrates, including pyridines, thiophenes, pyrroles and pyrazoles, giving the azocine RCM precursors in good overall yields. Furthermore, by exploiting the relative acidity of the *C*-allyl group, several substrates were successfully tautomerised into the styrenyl compounds by treatment with NaH (for pyridines) or *n*-BuLi. This approach is particularly useful as it allows both the azocine and azepine RCM products to be accessed from a single starting material and provides a useful alternative to the traditional formylation/Wittig[15] and iodination/Stille[16] pathways to these substrates (Scheme 3).

We also wanted to evaluate benzylic examples (i.e., with the amide reduced), as such structures appear in several natural products (e.g., galanthamine, apparacine, see Fig. 1). Unfortunately, direct reduction of the amide did not prove to be a reliable reaction. Heating pyridine **1** with $LiAlH_4$ in THF was required to achieve the initial reduction of the amide, with the second reduction of the amino-alcohol intermediate being somewhat sluggish. Prolonged heating or addition of further reductant appeared to give products



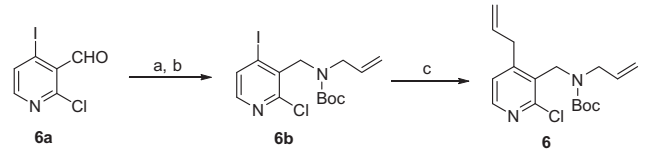
Scheme 2. Initial route to heterocycle-fused azocines and azepines. Reagents and conditions: (a) $(COCl)_2$, CH_2Cl_2, DMF (cat.), then allylamine, Et_3N; (b) allylamine, Et_3N, CH_2Cl_2; (c) *n*-BuLi, CuBr, allyl bromide, THF.



Scheme 3. Tautomerisation of *C*-allyl substrates.

consistent with over-reduction. Alternatively, attempted metallation/allylation of the benzylic CH_2N(Boc)allyl pyridine resulted largely in alkylation on the allylic methylene. The desired product was accessed eventually by reductive amination of 4-iodopyridine **6a** with allylamine followed by *N*-Boc protection to give **6b**, then a magnesium-halogen exchange with ^{i}PrMgCl[17] and quenching with allyl bromide to give **6** (Scheme 4). As with other examples, the 4-allyl moiety could be tautomerised to the styrene **7** by stirring with NaH in DMF.

With the precursors in hand, we began our studies into the RCM reaction. Table 1. Amido-pyridine **1** reacted sluggishly when treated with 5 mol% of Grubbs (II) catalyst in CH_2Cl_2, giving only traces of the RCM product **17** after heating to reflux for 4 h. Further heating to 80 °C in toluene gave mostly the competitive cross-metathesis product rather than the RCM product. Pleasingly, protection of the NH with either Boc or methyl did allow the RCM reaction to occur. *N*-Boc precursor **2** gave the azocine **17** in reasonable yield after Boc group cleavage (TFA in CH_2Cl_2), although significant amounts of the cross-metathesis product were still seen. The formation of this unwanted side-product could be suppressed to a degree by increasing the reaction dilution from 0.1 to 0.02 M (47% vs 60% yield of **17**), however further dilution was not attempted as it would limit the practicality of the reaction. Interestingly, *N*-Me precursor **3** reacted significantly more smoothly in the RCM reaction than the *N*-Boc compound **2**, giving methylated azocine **18** in an 81% yield, with only a small amount of the cross-metathesis product observed in the reaction mixture. Tautomerised pyridine **4** reacted more quickly in the RCM reaction than the allyl compound giving azepine **19** in a 63% yield after *N*-Boc cleavage. This is not entirely surprising as seven-membered ring formation is generally more favourable than eight-membered systems. When a methyl group was introduced onto the *C*-allyl (compound **5**), only cross-metathesis via the *N*-allyl was observed, highlighting the sensitivity of these substrates to steric contraints. The absence of the amide carbonyl in precursors **6** and **7** resulted in much smoother RCM reactions, giving azocine **21** and azepine **22**, respectively, in excellent yields (93% and 85%). Gratifyingly, sulfonamides **8** and **9** not only reacted smoothly in the RCM reaction without the need for *N*-protection, but they also tolerated a methylallyl moiety, giving methylated azocine **24** in an excellent 89% yield. The reaction was then extended to include five-membered heterocycles. Amido-thiophenes **10** and **11** worked reasonably well in the RCM, as did amido-furan **13**. As with the pyridine examples, the sulfonamide analogues reacted considerably more smoothly than the amide series, with thiophene **12**, pyrazole **14** and pyrrole **15** giving the sulfonamide azocines in high yields (70–84%). Sulfonamido-azaindole **16** appeared to react somewhat slowly in the RCM, requiring prolonged heating for 16 h to achieve a 25% conversion into tricyclic azocine **31**.



Scheme 4. Reagents and conditions: (a) allylamine, MeOH, rt, then $NaBH_4$, 77%; (b) Boc_2O, MeOH, rt, 91%; (c) ^{i}PrMgCl, THF, −30 °C–rt, then allyl bromide, 70%.